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Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study

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Summary

Background The relationship between macronutrients and cardiovascular disease and mortality is controversial. Most available data are from European and North American populations where nutrition excess is more likely, so their applicability to other populations is unclear.

Methods The Prospective Urban Rural Epidemiology (PURE) study is a large, epidemiological cohort study of individuals aged 35–70 years (enrolled between Jan 1, 2003, and March 31, 2013) in 18 countries with a median follow-up of 7·4 years (IQR 5·3–9·3). Dietary intake of 135 335 individuals was recorded using validated food frequency questionnaires. The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. Participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy provided by nutrients. We assessed the associations between consumption of carbohydrate, total fat, and each type of fat with cardiovascular disease and total mortality. We calculated hazard ratios (HRs) using a multivariable Cox frailty model with random intercepts to account for centre clustering.

Findings During follow-up, we documented 5796 deaths and 4784 major cardiovascular disease events. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] *vs* lowest quintile [quintile 1] category, HR 1·28 [95% CI 1·12–1·46], p_{trend}=0·0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 *vs* quintile 1, total fat: HR 0·77 [95% CI 0·67–0·87], p_{trend}<0·0001; saturated fat, HR 0·86 [0·76–0·99], p_{trend}=0·0088; monounsaturated fat: HR 0·81 [0·71–0·92], p_{trend}<0·0001; and polyunsaturated fat: HR 0·80 [0·71–0·89], p_{trend}<0·0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 *vs* quintile 1, HR 0·79 [95% CI 0·64–0·98], p_{trend}=0·0498). Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality.

Interpretation High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke. Global dietary guidelines should be reconsidered in light of these findings.

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Introduction

Cardiovascular disease is a global epidemic with 80% of the burden of disease in low-income and middle-income countries.[1] Diet is one of the most important modifiable risk factors for cardiovascular disease and other non-communicable diseases and current guidelines recommend a low-fat diet (<30% of energy) and limiting saturated fatty acids to less than 10% of energy intake by replacing them with unsaturated fatty acids.[2] However, recommendations on lowering saturated fatty acids are largely based on one ecological study[3] and observational studies done in European and North American countries such as Finland, where the intake of saturated fatty acids (about 20% of total energy intake) and cardiovascular disease mortality were both very high.[4] Furthermore, dietary recommendations are based on the assumption of a linear association between saturated fatty acid intake and LDL cholesterol, and then the association between LDL cholesterol and cardiovascular disease events. However, this assumption does not consider the effect of saturated fatty acids on other lipoproteins (eg, HDL cholesterol), ratio of total

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Research in context

Evidence before this study

We did a systematic search in PubMed for relevant articles published between Jan 1, 1960, and May 1, 2017, restricted to the English language. Our search terms included "carbohydrate", "total fat", "saturated fatty acid", "monounsaturated fatty acid", "polyunsaturated fatty acid", "total mortality", and "cardiovascular disease". We searched published articles by title and abstract to identify relevant studies. We also hand-searched reference lists of eligible studies. We considered studies if they evaluated association between macronutrient intake and total mortality or cardiovascular disease. The studies cited in this report are not an exhaustive list of existing research. Existing evidence on the associations of fats and carbohydrate intake with cardiovascular disease and mortality are mainly from North America and Europe.

Added value of this study

Current guidelines recommend a low fat diet (<30% of energy) and limiting saturated fatty acids to less than 10% of energy intake by replacing them with unsaturated fatty acids. The recommendation is based on findings from some North American and European countries where nutrition excess is of concern. It is not clear whether this can be extrapolated to other countries where undernutrition is common. Moreover, North American and European populations consume a lower carbohydrate diet than populations elsewhere where most people consume very high carbohydrate diets mainly from refined sources. Consistent with most data, but in contrast to dietary guidelines, we found fats, including saturated fatty acids, are not harmful and diets high in carbohydrate have adverse effects on total mortality. We did not observe any detrimental effect of higher fat intake on cardiovascular events. Our data across 18 countries adds to the large and growing body of evidence that increased fats are not associated with higher cardiovascular disease or mortality.

Implications of all the available evidence

Removing current restrictions on fat intake but limiting carbohydrate intake (when high) might improve health. Dietary guidelines might need to be reconsidered in light of consistent findings from the present study, especially in countries outside of Europe and North America.

cholesterol to HDL cholesterol, or on apolipoproteins (which could be a better marker of cardiovascular disease risk)[5,6] and blood pressure, which also affect the risk of cardiovascular disease.[7]

Recently, several meta-analyses of randomised trials and prospective cohort studies[8–10] and ecological studies,[11] largely done in European and North American countries, showed either no association or a lower risk between saturated fatty acid consumption with total mortality and cardiovascular disease events.[12,13] The uncertainty regarding the effect of saturated fatty acids on clinical outcomes in part might be due to the fact that most observational cohort studies have been done in high-income countries[8,9] where saturated fatty acid intake is within a limited range (about 7–15% of energy). Furthermore, it is not known whether findings obtained from European and North American countries where nutritional excess is more common, can be extrapolated to other regions of the world where nutritional inadequacy might be more common. The Prospective Urban Rural Epidemiology (PURE) study provides a unique opportunity to study the impact of diet on total mortality and cardiovascular disease in diverse settings, such as those where overnutrition is common and where undernutrition is of greater concern. In this study, our primary aim was to assess the association of fats (total, saturated fatty acids, and unsaturated fats) and carbohydrate with total mortality and cardiovascular disease events. The secondary aim was to examine associations between these nutrients and myocardial infarction, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality.

Methods

Study design and participants

The design and methods of the PURE study have been described previously.[1,14–16] PURE recruitment occurred between Jan 1, 2003, and March 31, 2013, and included individuals aged 35–70 years from 18 low-income, middle-income, and high-income countries on five continents. We aimed to include populations that varied by socioeconomic factors while ensuring feasibility of long-term follow-up when selecting the participating countries. We included three high-income (Canada, Sweden, and United Arab Emirates), 11 middle-income (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestinian territory, Poland, South Africa, and Turkey) and four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe), based on gross national income per capita from the World Bank classification for 2006 when the study was initiated. Additional countries have joined PURE, but since follow-up in these countries is incomplete, they are not included in the present analyses. The study was coordinated by the Population Health Research Institute (PHRI; Hamilton Health Sciences, Hamilton, ON, Canada). More details of the sampling and recruitment strategy used in PURE are detailed in the Article by Miller and colleagues[17] and an earlier report.[18]

Procedures

Data were collected at the community, household, and individual levels. Within participating communities, our goal was to enrol an unbiased sample of households. Households were eligible if at least one member was

between 35 and 70 years of age, and the household intended to stay in the current address for another 4 years. Standardised questionnaires were used to collect information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history, and medication use. Physical activity was assessed using the International Physical Activity Questionnaire.[19] History of diabetes was self-reported. Physical assessment included weight, height, waist and hip circumferences, and blood pressure. Detailed follow-up occurred at 3, 6, and 9 years and repeated measures of selected risk factors, causes of death, other health outcomes, and community data were collected. Standardised case-report forms were used to record data on major cardiovascular events and mortality during follow-up, which were adjudicated centrally in each country by trained physicians using standard definitions (appendix pp 8–17). Data were electronically transferred to the PHRI where quality control checks were undertaken.

Participants' habitual food intake was recorded using country-specific (or region-specific in India) validated food frequency questionnaires (FFQs) at baseline. Where a validated FFQ was not available (ie, Argentina), we developed and validated FFQs using a standard method.[20–30] Multiple 24-h dietary recalls were used as the reference method to validate the FFQs in about 60–250 participants from each country (appendix p 18). To convert food into nutrients, country-specific nutrient databases were constructed with information on 43 macronutrients and micronutrients. The nutrient databases are primarily based on the United States Department of Agriculture food composition database (release 18 and 21), modified with reference to local food composition tables, and supplemented with recipes of local mixed dishes.[31] However, for Canada, China, India, Malaysia, South Africa, Sweden, and Turkey we used the nutrient databases that were used for validation of the FFQs. The FFQ was administered together with other questionnaires at the baseline.

For the current analysis, we included all outcome events known to us until March 31, 2017. 148 723 participants completed the FFQ, of which 143 934 participants had plausible energy intake (500–5000 kcal per day) and had no missing values on age and sex. We excluded 1230 participants (0·8% of the cohort) because follow-up information was not available and 7369 participants with a history of cardiovascular disease (5·0% of the cohort). The remaining 135 335 individuals were included in this analysis (appendix p 19).

Outcomes

The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. The numbers of cases of heart failure were too few to be analysed separately.

The follow-up period varied based on the date when recruitment began at each site or country. During the follow-up period contact was made with every participant on an annual basis either by telephone or by a face-to-face interview with the local research team. The median duration of follow-up was 7·4 years (IQR 5·3–9·3), which varied across countries (appendix p 22).

Statistical analysis

Continuous variables were expressed as means (SDs) and categorical variables as percentages. Education was categorised as none, primary school (first 6 years), or secondary school (7–11 years) and college, trade school, or university (>11 years). Smoking was categorised as never, former, or current smoker. Physical activity was categorised based on the metabolic equivalent of task (MET) per min per week into low (<600 MET min per week), moderate (600–3000 MET min per week), and high (>3000 MET min per week) activity. Waist-to-hip ratio (waist circumferences [cm]/hip circumferences [cm]) was used as a continuous variable. Since food patterns are culture dependent and dietary patterns are generally related to geographical region rather than income region, we categorised countries into seven regions. Regions included China, south Asia (Bangladesh, India, and Pakistan), North America, Europe (Canada, Poland, and Sweden), South America (Argentina, Brazil, Chile, and Colombia), Middle East (Iran, occupied Palestinian territory, Turkey, and United Arab Emirates), southeast Asia (Malaysia), and Africa (South Africa and Zimbabwe). For the overall analysis, participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy (% E) provided by nutrients, which was computed by dividing energy from the nutrient by the total daily energy intake (eg, for carbohydrate, %E=([carbohydrate (g)×4]/total energy intake [kcal])×100). To assess the shape of associations between nutrients and events we used restricted cubic splines, fitting a restricted cubic spline function with three knots. We calculated hazard ratios (HRs) using a multivariable Cox frailty model with random intercepts to account for centre clustering (which also adjusts for region and country). Estimates of HRs and 95% CIs are presented for percentage of energy from carbohydrate, total protein, total fat, and types of fat. All models were adjusted for age and sex. Additionally, all multivariable models were adjusted for education, smoking, physical activity, waist-to-hip ratio, history of diabetes, urban or rural location, and total energy intake.

In subgroup analyses, since higher carbohydrate (but lower fat) consumption is more common in Asian countries[32,33] and lower carbohydrate intake (and higher fat) in non-Asian countries[11] we examined whether the

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See **Online** for appendix

effect of carbohydrate and fats on outcomes were consistent in these two regions. The countries in Asia included Bangladesh, China, India, Malaysia, and Pakistan; the remaining countries were considered to be non-Asian countries. We used this approach for two main reasons: to assess the consistency of the associations across regions representing different levels of nutrient intake, with Asian countries characterising higher carbohydrate (and lower fat) consumption and non-Asian countries capturing lower carbohydrate intake (and higher fat); and to maximise the power within regions (compared with examining effects within smaller geographical regions with fewer people and relatively few events). Participants were categorised into region-specific quintile categories of nutrient intake based on the intake distribution of participants in Asian and non-Asian countries, with the lowest quintile category used as reference group within regions (we did not do further region subgroup analyses due to low statistical power to detect subgroup interactions). Since the impact of macronutrient intake on outcome events might or might not occur through changes in waist-to-hip ratio, we excluded waist-to-hip ratio from the multivariable models in secondary analyses to assess the impact on estimates.

The effect of isocaloric replacement (as 5% of energy) of carbohydrate with saturated and unsaturated fats and protein was estimated using multivariable nutrient density models.[34] In this modelling approach, the percentage of energy intake from saturated and unsaturated fats and protein were included as exposures with total energy as a covariate. The coefficients in this model indicate change in outcomes by replacement of carbohydrate (as 5% of energy) by other nutrients. For all analyses, the criterion for statistical significance was $\alpha=0\cdot05$. Statistical analyses were done with SAS software, version 9.3. Spline curves were generated with the SAS LGTPHCURV9 Macro.

	Overall (n=135 335)	China (n=42 152)	South Asia (n=29 560)	Europe and North America (n=14 916)	South America (n=22 626)	Middle East (n=11 485)	Southeast Asia (n=10 038)	Africa (n=4558)
Age (years)	50·29 (9·92)	50·58 (9·82)	48·18 (10·24)	53·01 (9·18)	51·13 (9·69)	48·57 (9·23)	51·47 (9·96)	49·98 (10·35)
Male	56 422 (41·7%)	17 575 (41·7%)	12 887 (43·6%)	6567 (44·0%)	8685 (38·4%)	4930 (42·9%)	4323 (43·1%)	1455 (31·9%)
Urban location	71 300 (52·7%)	20 170 (47·9%)	14 224 (48·1%)	10 488 (70·3%)	12 896 (57·0%)	6526 (56·8%)	4841 (48·2%)	2155 (47·3%)
Systolic blood pressure (mm Hg)	130·9 (22·2)	132·9 (22·2)	125·8 (21·2)	132·0 (20·4)	131·7 (22·7)	127·1 (20·3)	135·2 (23·1)	138·9 (27·5)
Waist-to-hip ratio	0·87 (0·08)	0·86 (0·07)	0·87 (0·09)	0·88 (0·09)	0·890 (0·08)	0·89 (0·09)	0·83 (0·08)	0·84 (0·087)
Current smoker	28 410/134 449 (21·1%)	9588/41 670 (23·0%)	6799/29 468 (23·1%)	2256/14 888 (15·2%)	4709/22 548 (20·9%)	2178/11 485 (19·0%)	1532/9943 (15·4%)	1348/4447 (30·3%)
Education								
Pre-secondary school	57 438/134 981 (42·6%)	14 113/42 036 (33·6%)	15 135/29 432 (51·4%)	1138/14 903 (7·6%)	13 298/22 565 (58·9%)	6935/11 485 (60·4%)	4263/10 032 (42·5%)	2556/4528 (56·5%)
Secondary school	51 730/134 981 (38·3%)	21 853/42 036 (52·0%)	10 239/29 432 (34·8%)	4649/14 903 (31·2%)	5471/22 565 (24·3%)	3114/11 485 (27·1%)	4551/10 032 (45·4%)	1853/4528 (40·9%)
Post-secondary school	25 813/134 981 (19·1%)	6070/42 036 (14·4%)	4058/29 432 (13·8%)	9116/14 903 (61·2%)	3796/22 565 (16·8%)	1436/11 485 (12·5%)	1218/10 032 (12·1%)	119/4528 (2·6%)
Physical activity								
Low (<600 MET per min per week)	22 022/125 945 (17·5%)	6424/41 534 (15·5%)	5588/25 999 (21·5%)	826/13 628 (6·1%)	2889/21 567 (13·4%)	2452/11 342 (21·6%)	3315/9428 (35·2%)	528/2447 (21·6%)
Moderate (600–3000 MET per min per week)	47 850/125 945 (38·0%)	17 518/41 534 (42·2%)	8903/25 999 (34·2%)	4757/13 628 (34·9%)	6944/21 567 (32·2%)	5290/11 342 (46·6%)	3336/9428 (35·4%)	1102/2447 (45·0%)
High (>3000 MET per min per week)	56 073/125 945 (44·5%)	17 592/41 534 (42·4%)	11 508/25 999 (44·3%)	8045/13 628 (59·0%)	11 734/21 567 (54·4%)	3600/11 342 (31·7%)	2777/9428 (29·5%)	817/2447 (33·4%)
History of diabetes	9634 (7·1%)	1610 (3·8%)	2723 (9·2%)	785 (5·3%)	1530 (6·8%)	1405 (12·2%)	1351 (13·5%)	230 (5·1%)
Energy from carbohydrate (%)	61·2% (11·6)	67·0% (9·8)	65·4% (11·3)	52·4% (8·1)	57·6% (11·4)	53·5% (7·5)	53·9% (8·2)	63·3% (11·5)
Energy from fat (%)	23·5% (9·3)	17·7% (7·8)	22·7% (10·4)	30·5% (6·0)	25·2% (7·7)	30·3% (6·1)	29·2% (5·9)	22·8% (8·3)
Energy from protein (%)	15·2% (3·6)	15·3% (2·3)	11·6% (1·9)	16·7% (2·7)	17·5% (3·8)	16·9% (2·8)	17·1% (3·2)	13·4% (3·0)
Energy from saturated fatty acids (%)	8·0% (4·1)	5·7% (2·7)	8·4% (5·2)	10·9% (3·7)	8·9% (3·4)	10·2% (2·9)	9·2% (2·1)	5·9% (2·8)
Energy from monounsaturated fatty acids (%)	8·1% (3·7)	6·8% (2·9)	5·9% (3·1)	11·2% (2·6)	9·0% (3·2)	10·2% (3·0)	11·8% (3·9)	7·2% (3·2)
Energy from polyunsaturated fatty acids (%)	5·3% (3·0)	4·2% (2·8)	6·2% (4·0)	4·8% (1·3)	4·4% (1·6)	7·0% (1·9)	8·2% (2·0)	6·0% (2·9)
Energy from protein (%)	15·2% (3·6)	15·3% (2·8)	11·7% (1·9)	16·7% (2·7)	17·5% (3·8)	16·9% (2·8)	17·2% (3·2)	13·4% (3·0)
Energy from animal protein (%)	6·4% (4·5)	5·6% (3·4)	1·9% (1·9)	9·3% (3·0)	10·5% (4·9)	8·9% (3·0)	7·3% (3·1)	5·2% (3·1)
Energy from plant protein (%)	8·8% (2·2)	9·7% (1·5)	9·8% (2·1)	7·4% (2·0)	7·0% (2·3)	8·0% (1·3)	9·8% (2·2)	7·5% (1·4)

Data are mean (SD), n (%), or n/N (%). MET=metabolic equivalents.

Table 1: **Characteristics of the study participants at baseline by region and overall**

Role of the funding sources

The funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. MD, AM, XZ, SR, SIB, SSA, and SY had full access to the data and were responsible for the decision to submit for publication.

Results

During a median follow-up of 7·4 years (IQR 5·3–9·3), 5796 individuals died and 4784 had a major cardiovascular disease event (2143 myocardial infarctions and 2234 strokes).

	Incidence (per 1000 person-years; 95% CI)					Hazard ratio (95% CI)				p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 2 *vs* quintile 1	Quintile 3 *vs* quintile 1	Quintile 4 *vs* quintile 1	Quintile 5 *vs* quintile 1	
Percentage energy from carbohydrate										
Median (IQR)	46·4% (42·6–49·0)	54·6% (52·9–56·2)	60·8% (59·3–62·3)	67·7% (65·7–69·7)	77·2% (74·4–80·7)	..	..	..	..	..
Total mortality	4·1 (3·8–4·3)	4·2 (3·9–4·5)	4·5 (4·2–4·8)	4·9 (4·6–5·2)	7·2 (6·9–7·5)	1·07 (0·96–1·20)	1·06 (0·94–1·19)	1·17 (1·03–1·32)	1·28 (1·12–1·46)	0·0001
Major cardiovascular disease	3·9 (3·6–4·2)	4·2 (3·9–4·5)	4·2 (3·9–4·5)	4·6 (4·3–4·8)	5·1 (4·8–5·4)	1·00 (0·90–1·12)	1·02 (0·91–1·14)	1·08 (0·96–1·22)	1·01 (0·88–1·15)	0·62
Myocardial infarction	2·0 (1·8–2·2)	2·2 (2·0–2·4)	2·0 (1·8–2·2)	1·8 (1·6–2·0)	2·1 (1·9–2·3)	0·93 (0·80–1·09)	0·92 (0·78–1·09)	0·99 (0·83–1·18)	0·90 (0·73–1·10)	0·40
Stroke	1·4 (1·3–1·6)	1·6 (1·4–1·7)	1·8 (1·6–2·0)	2·4 (2·2–2·6)	2·7 (2·5–2·9)	1·03 (0·86–1·22)	1·09 (0·91–1·31)	1·21 (1·01–1·45)	1·11 (0·92–1·35)	0·10
Cardiovascular disease mortality	1·3 (1·1–1·4)	1·6 (1·4–1·7)	1·4 (1·3–1·6)	1·3 (1·2–1·5)	1·7 (1·5–1·9)	1·18 (0·97–1·43)	1·02 (0·83–1·26)	1·11 (0·88–1·38)	1·13 (0·89–1·44)	0·50
Non-cardiovascular disease mortality	2·5 (2·3–2·7)	2·3 (2·1–2·5)	2·7 (2·5–2·9)	3·2 (3·0–3·5)	5·1 (4·8–5·4)	1·00 (0·87–1·15)	1·09 (0·94–1·27)	1·22 (1·05–1·42)	1·36 (1·16–1·60)	<0·0001
Percentage energy from total fat										
Median (IQR)	10·6% (8·1–12·6)	18·0% (16·3–19·7)	24·2% (22·8–25·5)	29·1% (27·9–30·3)	35·3% (33·3–38·3)	..	..	..	..	..
Total mortality	6·7 (6·4–7·0)	5·1 (4·7–5·4)	4·6 (4·3–5·0)	4·3 (4·0–4·6)	4·1 (3·9–4·4)	0·90 (0·82–0·98)	0·81 (0·73–0·90)	0·80 (0·71–0·90)	0·77 (0·67–0·87)	<0·0001
Major cardiovascular disease	5·3 (5·0–5·6)	4·3 (4·0–4·6)	4·2 (3·9–4·5)	4·0 (3·8–4·3)	4·1 (3·8–4·4)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·95 (0·84–1·07)	0·95 (0·83–1·08)	0·33
Myocardial infarction	2·1 (1·9–2·3)	1·6 (1·4–1·8)	2·0 (1·8–2·2)	2·0 (1·8–2·2)	2·3 (2·1–2·6)	1·02 (0·87–1·20)	1·08 (0·90–1·29)	0·97 (0·80–1·18)	1·12 (0·92–1·37)	0·40
Stroke	3·0 (2·7–3·2)	2·3 (2·1–2·6)	1·6 (1·5–1·8)	1·6 (1·4–1·8)	1·3 (1·2–1·5)	1·05 (0·93–1·19)	0·91 (0·78–1·06)	0·95 (0·79–1·13)	0·82 (0·68–1·00)	0·05
Cardiovascular disease mortality	1·6 (1·4–1·8)	1·3 (1·2–1·5)	1·5 (1·3–1·6)	1·4 (1·3–1·6)	1·5 (1·3–1·7)	0·89 (0·74–1·06)	0·92 (0·75–1·12)	0·88 (0·70–1·10)	0·92 (0·72–1·16)	0·50
Non-cardiovascular disease mortality	4·7 (4·4–5·0)	3·4 (3·1–3·6)	2·9 (2·6–3·1)	2·6 (2·3–2·8)	2·3 (2·1–2·5)	0·91 (0·82–1·01)	0·78 (0·69–0·89)	0·78 (0·67–0·90)	0·70 (0·60–0·82)	<0·0001
Percentage energy from total protein										
Median (IQR)	10·8% (9·9–11·5)	13·1% (12·6–13·6)	15·0% (14·5–15·5)	16·9% (16·4–17·4)	19·7% (18·8–21·4)	..	..	..	..	..
Total mortality	8·5 (8·1–8·9)	5·4 (5·1–5·7)	3·7 (3·5–4·0)	3·2 (2·9–3·4)	3·6 (3·3–3·9)	1·05 (0·96–1·15)	0·92 (0·82–1·03)	0·85 (0·75–0·96)	0·88 (0·77–1·00)	0·0030
Major cardiovascular disease	5·0 (4·7–5·3)	4·6 (4·3–4·9)	4·4 (4·1–4·7)	4·2 (3·9–4·5)	3·7 (3·5–4·0)	1·02 (0·91–1·13)	1·08 (0·96–1·22)	1·09 (0·97–1·24)	0·96 (0·84–1·10)	0·86
Myocardial infarction	2·8 (2·5–3·0)	2·0 (1·8–2·2)	1·7 (1·5–1·9)	1·7 (1·5–1·9)	1·7 (1·5–1·9)	1·04 (0·89–1·20)	1·01 (0·85–1·20)	1·11 (0·92–1·33)	1·02 (0·83–1·24)	0·67
Stroke	1·8 (1·6–2·0)	2·2 (2·0–2·4)	2·4 (2·1–2·6)	2·1 (1·9–2·3)	1·6 (1·4–1·8)	1·01 (0·86–1·19)	1·14 (0·96–1·36)	1·11 (0·92–1·33)	0·90 (0·74–1·09)	0·47
Cardiovascular disease mortality	2·4 (2·2–2·6)	1·7 (1·5–1·9)	1·0 (0·9–1·2)	0·9 (0·8–1·1)	1·1 (0·9–1·2)	1·09 (0·93–1·29)	0·89 (0·73–1·10)	0·92 (0·74–1·16)	0·90 (0·71–1·15)	0·26
Non-cardiovascular disease mortality	5·5 (5·2–5·8)	3·3 (3·1–3·6)	2·5 (2·2–2·7)	2·0 (1·8–2·2)	2·3 (2·1–2·5)	1·02 (0·91–1·15)	0·92 (0·80–1·05)	0·79 (0·68–0·93)	0·85 (0·73–0·99)	0·0022

Hazard ratios and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Table 2: **Association between percentage energy from macronutrients and clinical outcomes (n=135 335)**

1649 died due to cardiovascular disease and 3809 died due to non-cardiovascular disease. There were 338 deaths due to injury, which were not included in non-cardiovascular disease mortality because these were considered to be unlikely to be associated with diet. Among non-cardiovascular disease mortality, in all regions except Africa, the most common cause of mortality was cancer followed by respiratory diseases. In Africa, infectious disease was the first and respiratory disease was the second most common cause of non-cardiovascular disease mortality.

The characteristics of participants and data on macronutrient intake are presented in table 1.

Carbohydrate intake was higher in China, south Asia, and Africa compared with other regions. In south Asia about

	Incidence (per 1000 person-years; 95% CI)					Hazard ratio (95% CI)				p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 2 *vs* quintile 1	Quintile 3 *vs* quintile 1	Quintile 4 *vs*· quintile 1	Quintile 5 *vs* quintile 1	
Percentage energy from saturated fatty acids										
Median (IQR)	2·8% (2·0–3·4)	4·9% (4·4–5·5)	7·1% (6·5–7·7)	9·5% (8·9–10·2)	13·2% (11·9–15·1)	..	..	..	..	..
Total mortality	7·1 (6·7–7·4)	5·2 (4·9–5·5)	4·3 (4·0–4·6)	3·9 (3·6–4·2)	4·4 (4·1–4·7)	0·96 (0·88–1·05)	0·92 (0·83–1·02)	0·85 (0·75–0·95)	0·86 (0·76–0·99)	0·0088
Major cardiovascular disease	5·2 (4·9–5·5)	4·7 (4·4–5·1)	4·1 (3·8–4·4)	3·9 (3·6–4·2)	4·1 (3·8–4·4)	1·13 (1·02–1·25)	1·06 (0·95–1·18)	1·03 (0·91–1·17)	0·95 (0·83–1·10)	0·49
Myocardial infarction	2·1 (1·9–2·3)	1·8 (1·6–2·0)	1·7 (1·5–1·9)	1·9 (1·7–2·1)	2·5 (2·3–2·7)	1·28 (1·08–1·51)	1·20 (1·00–1·44)	1·16 (0·95–1·41)	1·17 (0·94–1·45)	0·40
Stroke	2·7 (2·5–2·9)	2·6 (2·3–2·8)	1·9 (1·7–2·1)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·10 (0·97–1·25)	1·01 (0·87–1·17)	0·93 (0·78–1·11)	0·79 (0·64–0·98)	0·0498
Cardiovascular disease mortality	1·7 (1·6–1·9)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·4 (1·2–1·5)	1·4 (1·2–1·6)	1·04 (0·87–1·24)	0·95 (0·78–1·17)	0·99 (0·79–1·23)	0·83 (0·65–1·07)	0·20
Non-cardiovascular disease mortality	4·9 (4·6–5·2)	3·4 (3·1–3·6)	2·8 (2·5–3·0)	2·3 (2·1–2·5)	2·6 (2·4–2·8)	0·94 (0·84–1·04)	0·91 (0·81–1·03)	0·78 (0·68–0·91)	0·86 (0·73–1·01)	0·0108
Percentage energy from monounsaturated fatty acids										
Median (IQR)	3·4% (2·4–4·0)	5·4% (5·0–5·9)	7·3% (6·8–7·8)	9·5% (8·9–10·1)	12·5% (11·5–13·8)	..	..	..	..	..
Total mortality	7·5 (7·2–7·9)	5·6 (5·3–5·9)	4·4 (4·1–4·7)	3·7 (3·4–4·0)	3·7 (3·4–3·9)	1·02 (0·93–1·11)	0·91 (0·82–1·00)	0·81 (0·72–0·91)	0·81 (0·71–0·92)	<0·0001
Major cardiovascular disease	5·2 (4·9–5·5)	4·6 (4·3–4·9)	4·5 (4·2–4·8)	3·9 (3·6–4·2)	3·8 (3·6–4·1)	1·04 (0·94–1·15)	1·06 (0·95–1·18)	1·02 (0·90–1·15)	0·95 (0·84–1·09)	0·54
Myocardial infarction	2·4 (2·2–2·7)	2·0 (1·8–2·2)	1·9 (1·7–2·1)	1·8 (1·6–2·0)	1·9 (1·7–2·1)	1·09 (0·93–1·28)	1·13 (0·95–1·34)	1·04 (0·86–1·25)	1·12 (0·92–1·38)	0·40
Stroke	2·5 (2·3–2·7)	2·3 (2·1–2·5)	2·1 (1·9–2·3)	1·6 (1·5–1·8)	1·5 (1·3–1·6)	1·03 (0·90–1·18)	1·00 (0·86–1·16)	0·99 (0·83–1·17)	0·85 (0·70–1·03)	0·10
Cardiovascular disease mortality	1·9 (1·7–2·1)	1·7 (1·5–1·8)	1·4 (1·3–1·6)	1·3 (1·1–1·4)	1·1 (0·9–1·2)	1·07 (0·90–1·26)	0·98 (0·81–1·18)	0·90 (0·73–1·12)	0·85 (0·66–1·09)	0·10
Non-cardiovascular disease mortality	5·2 (4·9–5·5)	3·5 (3·3–3·8)	2·6 (2·4–2·8)	2·2 (2·0–2·4)	2·4 (2·1–2·6)	1·00 (0·90–1·11)	0·86 (0·76–0·97)	0·77 (0·67–0·89)	0·79 (0·68–0·93)	0·0003
Percentage energy from polyunsaturated fatty acids										
Median (IQR)	2·1% (1·6–2·5)	3·3% (3·1–3·6)	4·4% (4·1–4·7)	5·7% (5·4–6·2)	8·5% (7·5–10·4)	..	..	..	..	..
Total mortality	5·8 (5·5–6·2)	4·8 (4·5–5·1)	4·6 (4·3–4·9)	5·0 (4·6–5·3)	4·9 (4·6–5·2)	0·92 (0·84–1·01)	0·87 (0·79–0·96)	0·85 (0·77–0·94)	0·80 (0·71–0·89)	<0·0001
Major cardiovascular disease	5·4 (5·1–5·8)	3·9 (3·6–4·2)	4·0 (3·7–4·3)	4·2 (3·9–4·5)	4·7 (4·4–5·0)	1·01 (0·91–1·11)	0·99 (0·89–1·10)	0·97 (0·87–1·09)	1·01 (0·90–1·14)	0·94
Myocardial infarction	2·2 (2·0–2·4)	1·6 (1·4–1·8)	1·7 (1·6–1·9)	2·0 (1·8–2·2)	2·7 (2·4–2·9)	1·02 (0·86–1·21)	1·05 (0·88–1·25)	0·98 (0·82–1·17)	1·12 (0·93–1·34)	0·40
Stroke	3·0 (2·8–3·2)	1·9 (1·7–2·1)	1·7 (1·6–1·9)	1·7 (1·5–1·9)	1·6 (1·5–1·8)	0·96 (0·84–1·09)	0·94 (0·81–1·08)	0·95 (0·81–1·11)	0·92 (0·78–1·09)	0·30
Cardiovascular disease mortality	1·5 (1·3–1·6)	1·3 (1·1–1·5)	1·3 (1·2–1·5)	1·4 (1·2–1·6)	1·9 (1·7–2·1)	0·99 (0·82–1·19)	0·88 (0·72–1·07)	0·81 (0·67–0·99)	0·94 (0·76–1·15)	0·20
Non-cardiovascular disease mortality	4·0 (3·7–4·3)	3·2 (3·0–3·5)	3·0 (2·7–3·2)	3·2 (3·0–3·5)	2·6 (2·4–2·8)	0·90 (0·80–1·00)	0·86 (0·76–0·96)	0·88 (0·78–0·99)	0·75 (0·65–0·86)	0·0002

Hazard ratios and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Table 3: **Association between percentage energy from types of different fat and clinical outcomes (n=135 335)**

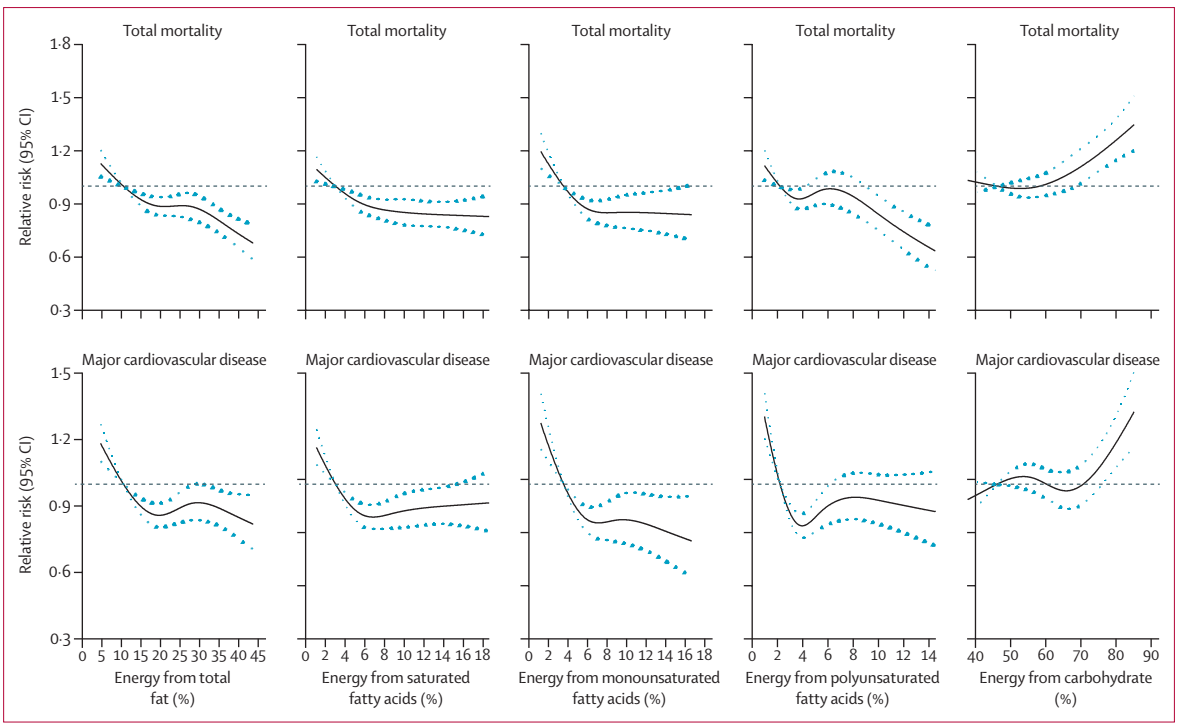

Figure 1: **Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135 335)**
Adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, centre, geographical regions, and energy intake. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

65% of the population consume at least 60% of energy from carbohydrate and 33% consume at least 70% of energy from carbohydrate, and in China the corresponding percentages are 77% and 43% (appendix p 33). The highest amount of fat consumed was in North America and Europe, Middle East, and southeast Asia. Intake of protein was highest in South America and southeast Asia.

Tables 2 and 3 show nutrient intake and risk of total mortality and cardiovascular disease events. Higher carbohydrate intake was associated with higher risk of total mortality (quintile 5 *vs* quintile 1, HR 1·28 [95% CI 1·12–1·46]; p_{trend}=0·0001) and non-cardiovascular disease mortality (quintile 5 *vs* quintile 1, HR 1·36 [1·16–1·60]; p_{trend}<0·0001), after multivariable adjustment for co-variates (table 2). No significant associations between carbohydrate intake and major cardiovascular disease, myocardial infarction, stroke, and cardiovascular disease mortality were recorded (table 2).

In comparisons between quintile 5 and quintile 1, total fat intake was associated with lower risks of total mortality (HR 0·77 [95% CI 0·67–0·87]; p_{trend}<0·0001), stroke (HR 0·82 [0·68–1·00]; p_{trend}=0·0562), and non-cardiovascular disease mortality (HR 0·70 [0·60–0·82]; p_{trend}<0·0001). No significant associations between total fat intake and major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality were found. Similarly, total protein intake was inversely associated with risks of total mortality (HR 0·88 [95% CI 0·77–1·00]; p_{trend}=0·0030) and non-cardiovascular disease mortality (HR 0·85 [0·73–0·99]; p_{trend}=0·0022; table 2). Animal protein intake was associated with lower risk of total mortality and no significant association was observed between plant protein and risk of total mortality.

In comparisons between quintile 5 and quintile 1, a higher intake of saturated fatty acids was inversely associated with risk of total mortality (HR 0·86 [95% CI 0·76–0·99]; p_{trend}=0·0088), stroke (HR 0·79 [0·64–0·98]; p_{trend}=0·0498), and non-cardiovascular disease mortality (HR 0·86 [0·73–1·01]; p_{trend}=0·0108; table 3). Higher saturated fatty acid intake was not associated with major cardiovascular disease, myocardial infarction, or cardiovascular disease mortality. Similarly, mono-unsaturated fatty acid intake was associated with lower risk of total mortality (HR 0·81 [95% CI 0·71–0·92]; p_{trend}<0·0001), a non-significant trend for lower risk of stroke (HR 0·85 [0·70–1·03]; p_{trend}=0·10), and lower risk of non-cardiovascular disease mortality (HR 0·79 [0·68–0·92]; p_{trend}=0·0003). Intake of polyunsaturated fatty acids was associated with lower risk of total mortality (HR 0·80 [95% CI 0·71–0·89]; p_{trend}<0·0001) and non-cardiovascular disease mortality (HR 0·75 [0·65–0·86]; p_{trend}=0·0002). Intakes of monounsaturated fatty acids and polyunsaturated fatty acids were not significantly associated with major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality.

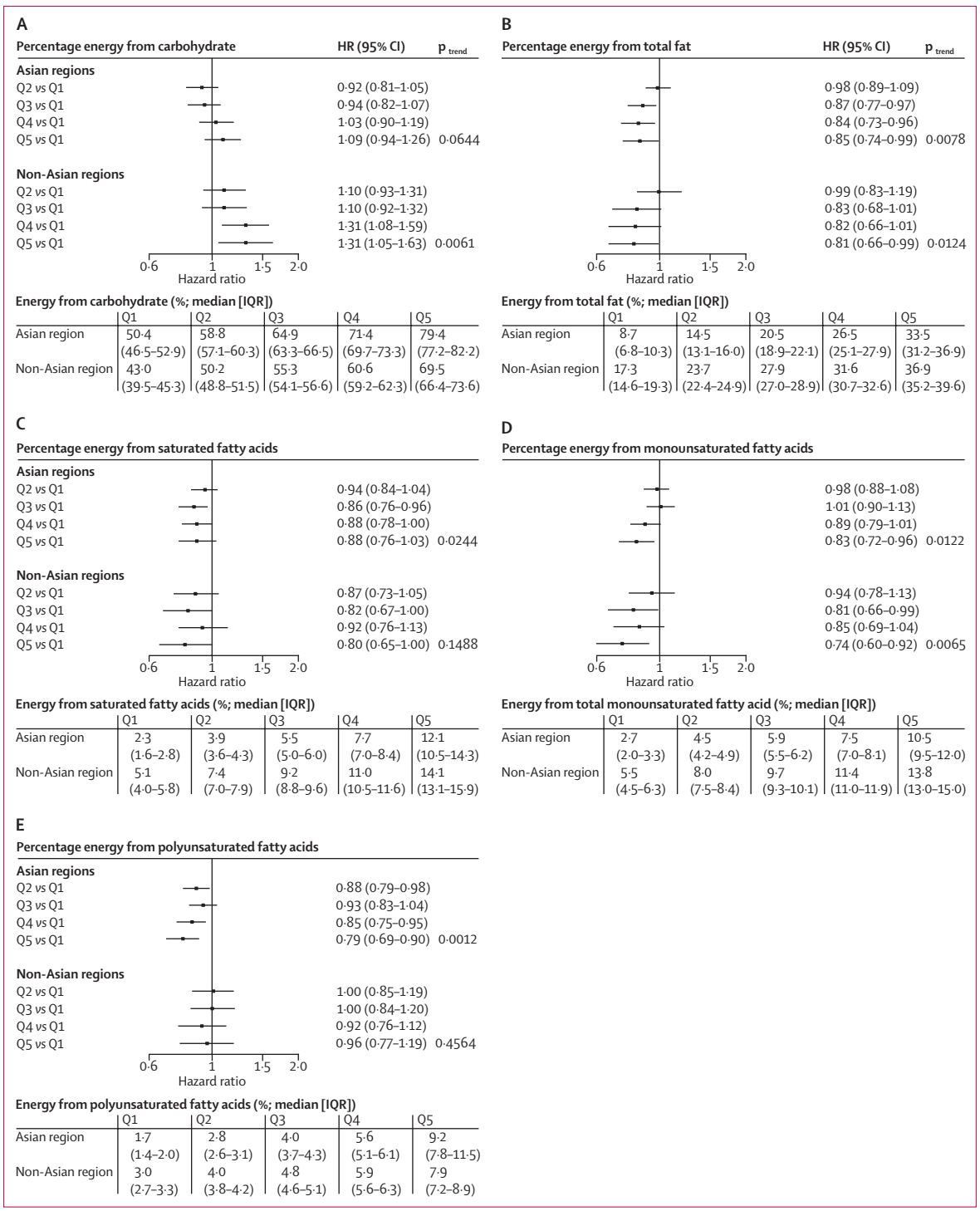

***Figure 2*: Associations between (A) carbohydrate, (B) total fat, (C) saturated fatty acids, (D) monounsaturated fatty acids, and (E) polyunsaturated fatty acids with risk of total mortality in Asia and other regions**

Hazard ratios (HRs) and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used (p for heterogeneity >0·2 for total fat and >0·5 for carbohydrate, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids). Q1–Q5=quintiles 1–5.

Restricted multivariable cubic spline plots for total mortality and major cardiovascular disease and other outcomes are shown in figure 1 and the appendix (pp 20, 21). Multivariable splines for total fats and subtypes

showed non-linear, decreasing trends in total mortality and major cardiovascular disease outcomes with increasing nutrients. However, multivariable splines for carbohydrate had a non-linear increasing trend in risks of total mortality and major cardiovascular disease (figure 1) and non-cardiovascular disease mortality (appendix p 21). The rise appeared to occur among those who consumed more than 60% (mid estimate from the spline) when energy intake from carbohydrate exceeded 70% energy (where the lower CI is above a HR of 1).

We investigated the influence of socioeconomic status and poverty using four different measures of socioeconomic status to adjust in the analysis of the associations between different nutrient intakes and total mortality and cardiovascular disease events. These were household wealth, household income, education, and economic level of the country subdivided by urban and rural locations. When we included education in the models, the estimates of association were robust. Additionally, we adjusted for study centre as a random effect which takes into account socioeconomic factors and clustering by community. When we reanalysed the data using household income, household wealth, or economic level of the country our results were unchanged (appendix p 34).

Higher carbohydrate intake was associated with higher risk of total mortality in both Asian countries and non-Asian countries (figure 2A). Conversely, higher intake of total fat and individual types of fat were each associated with lower total mortality risk in Asian countries and non-Asian countries (figure 2B–E).

Isocaloric (5% of energy) replacement of carbohydrate with polyunsaturated acids was associated with an 11% lower risk of mortality (HR 0·89 [95% CI 0·82–0·97]), whereas replacement of carbohydrate with saturated fatty acids, monounsaturated acids, or protein was not significantly associated with risk of total mortality. Replacement of carbohydrate with different types of fat or with protein was not significantly associated with major cardiovascular disease. Replacement of carbohydrate with saturated fatty acids was associated with a 20% lower risk of stroke (HR 0·80 [95% CI 0·69–0·93]). No significant associations with stroke risk were found for replacement of carbohydrate with other fats and protein. Replacement of carbohydrate with polyunsaturated fatty acids was associated with 16% lower risk of non-cardiovascular disease mortality (HR 0·84 [95% CI 0·76–0·94]; figure 3A–C).

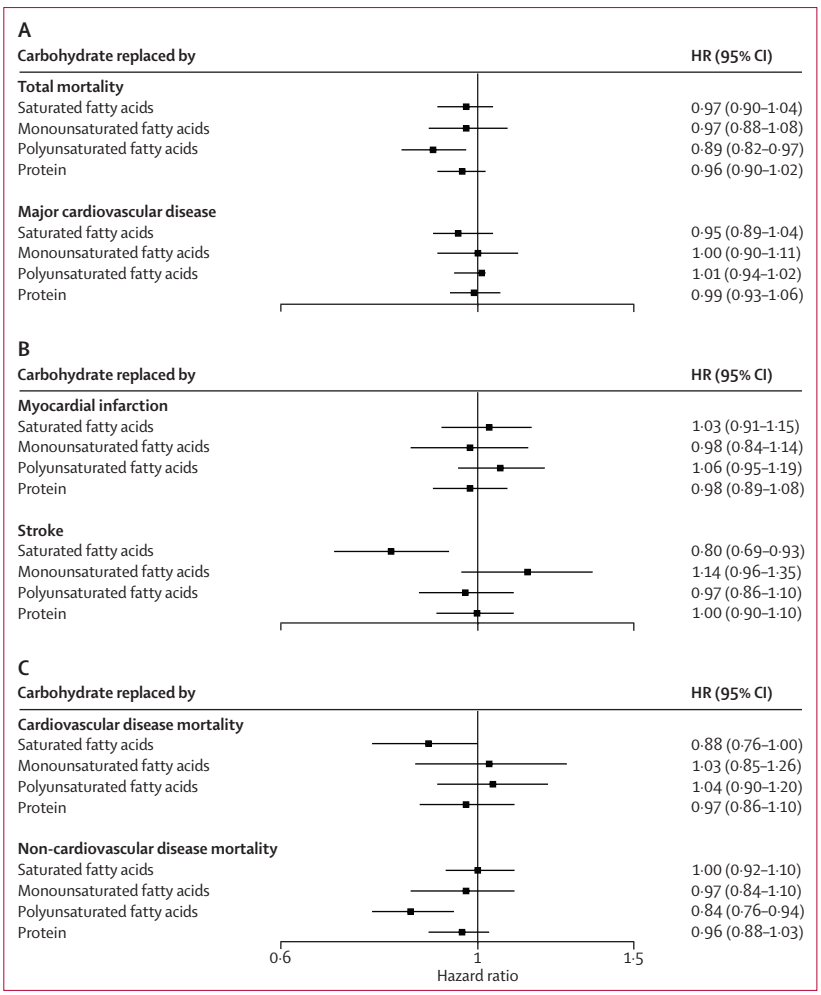

***Figure 3*: Risk of clinical outcomes associated with isocaloric (5% of energy) replacement of carbohydrate with other nutrients (n=135 335)**

Hazard ratios (HRs) and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Discussion

In this large prospective cohort study from 18 countries in five continents, we found that high carbohydrate intake (more than about 60% of energy) was associated with an adverse impact on total mortality and non-cardiovascular disease mortality. By contrast, higher fat intake was associated with lower risk of total mortality, non-cardiovascular disease mortality, and stroke. Furthermore, higher intakes of individual types of fat were associated with lower total mortality, non-cardiovascular disease mortality, and stroke risk and were not associated with risk of major cardiovascular disease events, myocardial infarction, or cardiovascular disease mortality. Our findings do not support the current recommendation to limit total fat intake to less than 30% of energy and saturated fat intake to less than 10% of energy. Individuals with high carbohydrate intake might benefit from a reduction in carbohydrate intake and increase in the consumption of fats.

For decades, dietary guidelines have focused on reducing total fat and saturated fatty acid intake, based on the presumption that replacing saturated fatty acids with carbohydrate and unsaturated fats will lower LDL cholesterol and should therefore reduce cardiovascular disease events. This focus is largely based on selective emphasis on some observational and clinical data,

despite the existence of several randomised trials and observational studies that do not support these conclusions.[9,35–37] Moreover, many studies that report higher risk of coronary heart disease deaths with higher saturated fatty acid intake were from North American and European populations (with relatively high intakes of total and saturated fats) where in the past cardiovascular disease was the major cause of deaths[38] and their applicability to other populations is uncertain.

In our study more than half of the participants (52%) consumed a high carbohydrate diet (at least 60% of energy) and about a quarter derive more than 70% of their energy from carbohydrate. This value is higher than most previous studies done in North America and Europe (appendix p 33). Furthermore, our study population represented a broad range of carbohydrate intake (mean intake of 46–77% of energy). This might explain the stronger association between carbohydrate intake and total mortality in our study compared with previous studies, which generally included participants with lower mean consumption of carbohydrate and a relatively narrower range of carbohydrate intake (35–56% of energy).[39–41] Moreover, in our study most participants from low-income and middle-income countries consumed a very high carbohydrate diet (at least 60% of energy), especially from refined sources (such as white rice and white bread), which have been shown to be associated with increased risk of total mortality and cardiovascular events.[42] Therefore, recommending lowering carbohydrate might be particularly applicable to such settings if replacement foods from fats and protein are available and affordable. It is also noteworthy that the spline plots showed a non-linear increasing trend in total mortality with a carbohydrate intake and the rise seems to occur among those who consumed more than 60% of energy from carbohydrate (ie, based on the midpoint of the estimate, with the lower CI showing an HR >0·1 when more than 70% of energy came from carbohydrates). Additionally, higher carbohydrate intakes increase some forms of dyslipidaemia (ie, higher triglycerides and lower HDL cholesterol), apolipoprotein B (ApoB)-to-apolipoprotein A1 (ApoA1) ratios and increased small dense LDL (the most atherogenic particles)[43,44] and increased blood pressure[45] (see Mente and colleagues[45]). However, the absence of association between low carbohydrate intake (eg, <50% of energy) and health outcomes does not provide support for very low carbohydrate diets. Importantly, a certain amount of carbohydrate is necessary to meet short-term energy demands during physical activity and so moderate intakes (eg, 50–55% of energy) are likely to be more appropriate than either very high or very low carbohydrate intakes.

A high carbohydrate diet is usually accompanied by a low fat intake. Our findings show a higher risk of total mortality, non-cardiovascular disease mortality, and stroke by lower fat consumption. The health benefit of replacing total fat with carbohydrate has been debated. Previous studies showed that replacement of fat with carbohydrate was not associated with lower risk of coronary heart disease and a pooled analysis of two large cohort studies (the Health Professionals Follow up and the Nurses' Health Study)[46] showed an inverse association between total fat and total mortality. Furthermore, higher glycaemic load was shown to be associated with a higher risk of ischaemic stroke in the Nurses' Health Study.[47] Our findings indicate that limiting total fat consumption is unlikely to improve health in populations, and a total fat intake of about 35% of energy with concomitant lowering of carbohydrate intake might lower risk of total mortality.

For individual fats, we found an inverse association between saturated fatty acid intake, total mortality, non-cardiovascular disease mortality, and stroke risk without any evidence of an increase in major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality. Our spline showed a non-linear association between saturated fatty acid intake and outcomes and this suggests that the nature of the relationship is more complex than previously assumed and the risks might depend on the amount of nutrient consumed. This is the first large study to describe the association between low level saturated fatty acid intake (eg, <7% of energy) and total mortality and cardiovascular disease events. Two large prospective cohort studies (the Health Professionals Follow up and the Nurses' Health Study) did not find significant associations between saturated fatty acid intake and risk of cardiovascular disease when replacement nutrients were not taken into account.[38,39,48,49] Randomised controlled trials of saturated fatty acid reduction (replaced by polyunsaturated fatty acids) have also not shown a statistically significant impact on total mortality.[9,35–37] Unlike previous studies from North American and European countries, our study covers a much broader range of saturated fatty acid intake including a large number of people in the lower range of intake (ie, 50% of participants consumed less than 7% of energy and 75% of participants consumed less than 10% of energy from saturated fatty acids compared with 50% of participants with greater than 10% of energy in studies of North American and European countries). The larger number of people (75%) with lower saturated fatty acids consumption in PURE allows us to examine the associations of low saturated fatty acids with total mortality and cardiovascular disease events. Our findings of an inverse association between saturated fatty acid intake and risk of stroke are consistent with some previous cohort studies.[50] Collectively, the available data[9] do not support the recommendation to limit saturated fatty acids to less than 10% of intake and that a very low intake (ie, below about 7% of energy) might even be harmful.

We found an inverse association between mono-unsaturated fatty acid intake and total mortality. Consistent with our findings, two large cohort studies of the Health Professionals Follow up and the Nurses' Health Study showed lower total mortality by higher monounsaturated fatty acid intake.[46] Furthermore, our

findings are consistent with randomised trials of the Mediterranean diet that have shown reduced risk of total mortality and cardiovascular disease among those consuming higher amounts of olive oil and nuts.[51] Higher polyunsaturated fatty acid intake was associated with lower total mortality rates and a modest lower risk of stroke. This finding is consistent with the lower total mortality among US men and women (the Health Professionals Follow up and the Nurses' Health Study) and Japanese men,[52] as well as a meta-analysis of randomised clinical trials.[53] Extensive adjustment for socioeconomic status using four different approaches (education, household income, household wealth, and income level of the country, with subdivision by rural and urban location) did not alter our results. Despite this, it is possible that high consumption of carbohydrate and low consumption of animal products might simply reflect lower incomes; residual confounding as a potential reason for our results cannot be completely excluded.

In our replacement analyses, the strongest association on total mortality was observed when carbohydrate was replaced with polyunsaturated fatty acids, which is consistent with the pooled analyses of the Health Professionals Follow up and the Nurses' Health Study.[46] We found a lower risk of stroke when carbohydrate was replaced with saturated fatty acids, which is consistent with previous work showing that refined carbohydrate intake is associated with increased risk of stroke.[7,47]

Mente and colleagues[45] relate the intake of total fat, types of fat, and carbohydrate to blood lipids and observed patterns of associations that were consistent with previous studies (eg, higher intakes of saturated fatty acids are associated with higher LDL cholesterol, but also with higher HDL cholesterol, lower triglycerides, lower total cholesterol-to-HDL cholesterol ratio, and lower ApoB-to-ApoA1 ratio). By contrast, increased carbohydrate intake is associated with lower LDL cholesterol but also with lower HDL cholesterol and higher triglycerides, total cholesterol-to-HDL cholesterol ratio, and ApoB-to-ApoA1 ratio. The latter is particularly noteworthy as ApoB-to-ApoA1 ratio is the strongest lipid predictor of myocardial infarction and ischaemic strokes; this might provide a mechanistic explanation for the higher risk of events seen with high carbohydrate intake and the generally lower risk of cardiovascular disease with greater saturated fatty acid intake. The lipid findings not only confirm the validity of the FFQs that we used in the PURE study, but also show that nutrients have varying effects on different lipid fractions. This suggests that predicting the net clinical effect based on considering only the effects of nutrient intake on LDL cholesterol is not reliable in projecting the effects of diet on cardiovascular disease events or on total mortality.

Our study is the first to our knowledge that used country-specific FFQs and nutrient databases in a large number of individuals from countries in diverse regions with varying food habits. The standardised dietary method enabled a direct comparison of nutrients and foods within each region included in the study and standardised methods to collect and adjudicate events. However, our study had some limitations. First, we used FFQs to estimate participants' dietary intake which is not a measure of absolute intake, but is suited for classifying individuals into intake categories and is the most commonly used approach for assessing intake in epidemiological studies. Measurement error in reporting might lead to random errors that could dilute real associations between nutrients and clinical events. Second, dietary intakes were measured only at baseline, and it is possible that dietary changes might have occurred during the follow-up period. Even if major dietary changes occurred after the baseline assessment, they probably would have weakened the observed associations. Third, there is potential for social desirability bias and individuals who are health conscious might also adopt other healthy lifestyles. However, if this were the case, we would not expect to see different associations for the different outcomes. Fourth, as with any observational cohort study, observed associations might be in part due to residual confounding (eg, differences in the ability to afford fats and animal proteins, which are more expensive than carbohydrates) despite extensive adjustment for known confounding factors. Furthermore, while high-carbohydrate and low-fat diets might be a proxy for poverty or access to health care, all of our models adjusted for education and study centre (which tracks with country income and urban or rural location) and would be expected to account for differences in socioeconomic factors across intake categories. Additional analyses adjusting for other measures of socioeconomic status (household wealth or income) did not alter the results. Despite this, it is possible that high consumption of carbohydrate and low consumption of animal products might reflect lower incomes and residual confounding of our results cannot be completely excluded. We were unable to quantify separately the types of carbohydrate (refined *vs* whole grains) consumed. However, carbohydrate consumption in low-income and middle-income countries is mainly from refined sources. Fifth, we were unable to measure trans-fat intake which might affect our results, especially our replacement analyses. Lastly, our FFQ assessed polyunsaturated fatty acid intake mainly from foods, rather than from vegetable oils, which might have different health effects than those observed in our study.

In conclusion, we found that a high carbohydrate intake was associated with an adverse impact on total mortality, whereas fats including saturated and unsaturated fatty acids were associated with lower risk of total mortality and stroke. We did not observe any detrimental effect of fat intakes on cardiovascular disease events. Global dietary guidelines should be reconsidered in light of the consistency of findings from the present study, with the conclusions from meta-analyses of other observational studies[8,10,54] and the results of recent randomised controlled trials.[36]

Contributors

MD coordinated the entire nutrition component of PURE, wrote the analysis plans, and had the primary responsibility for writing the paper. SY designed and supervised the PURE study, interpreted the data, and reviewed and commented on all drafts. AM reviewed and commented on the data analysis and drafts. XZ did the analysis and reviewed and commented on drafts. SSA reviewed and commented on the data analysis and drafts. SIB reviewed and commented on the data analysis. SR coordinated the worldwide study and reviewed and commented on drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

Declaration of interests

We declare no competing interests.

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PURE study challenges the definition of a healthy diet: but key questions remain

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The relationships between diet, cardiovascular disease, and death are topics of major public health importance, and subjects of great controversy.[1,2] In European and North American countries, the most enduring and consistent diet advice is to restrict saturated fatty acids, by replacing animal fats with vegetable oils and complex carbohydrates (and more recently whole grains).[1,3] In *The Lancet*, Mahshid Dehghan and colleagues[4] echo the views of a growing number of scientists by stating that advice to restrict saturated fatty acids "is largely based on selective emphasis on some observational and clinical data, despite the existence of several randomised trials and observational studies that do not support these conclusions". This lack of definitive evidence has left clinicians, scientists, and the public uncertain about the best foods to advise and to eat.[2]

Dehghan and colleagues[4] add to this uncertainty by publishing the initial results of the Prospective Urban Rural Epidemiology (PURE) study, an ambitious undertaking involving over 200 investigators who collected data on more than 135 000 individuals from 18 countries across five continents for an average of 7·4 years. As the largest prospective observational study to assess the association of nutrients (estimated by food frequency questionnaires) with cardiovascular disease and mortality in low-income and middle-income populations, the PURE findings make an important contribution to the field. The PURE team report that higher intakes of fats (including saturated fatty acids, monounsaturated fatty acids, and total polyunsaturated fatty acids) and animal protein were each associated with lower mortality, whereas carbohydrate intake was associated with increased mortality.[4] Here we provide context and highlight questions that need to be answered to move the field forward.

Do meats and dairy reduce mortality? Animal products (including beef, lamb, and dairy) are the major sources of saturated fatty acids and monounsaturated fatty acids in most populations studied in PURE. Since saturated fatty acids, monounsaturated fatty acids, and animal protein were all inversely associated with mortality, is the real finding simply that meat and dairy intakes were associated with increased survival? To answer this question, the PURE team needs to complete a thorough analysis relating intakes of different animal products to mortality.

Micronutrient malnutrition is an important problem in many of the countries included in PURE. Animal products are rich sources of zinc, bioavailable iron, vitamin K2, and vitamin B12, which might be suboptimal in populations consuming high carbohydrate diets. Therefore, one potential explanation for the PURE results is that nutrient-dense meats corrected one or more nutrient deficiencies. Since the PURE study collected blood for lipoprotein analyses,[5] this potential role of micronutrient deficiency in PURE could be investigated further.

Which carbohydrates are associated with increased mortality? Dehghan and colleagues[4] report that high intake of total carbohydrates was associated with increased mortality. In a concurrent *Lancet* Article,[6] the PURE group reports that intakes of fruits, legumes, and raw vegetables (three major carbohydrate sources) were associated with lower mortality. This discrepancy suggests that processed carbohydrates, including added sugars and refined grains, are likely driving this association. In a future paper, the PURE group should report associations between added sugars, refined grains, whole grains, and mortality.

Is PURE less confounded by conscientiousness than observational studies done in European and North

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American countries? Conscientiousness is among the best predictors of longevity.[7] For example, in a Japanese population, highly and moderately conscientious individuals had 54% and 50% lower mortality, respectively, compared with the least conscientious tertile.[8] Conscientious individuals exhibit numerous health-related behaviours ranging from adherence to physicians' recommendations and medication regimens,[9] to better sleep habits,[10] to less alcohol and substance misuse.[11] Importantly, conscientious individuals tend to eat more recommended foods and fewer restricted foods.[12] Since individuals in European and North American populations have, for many decades, received influential diet recommendations, protective associations attributed to nutrients in studies of these populations are likely confounded by numerous other healthy behaviours. Because many of the populations included in PURE are less exposed to influential diet recommendations, the present findings are perhaps less likely to be confounded by conscientiousness.

The PURE study is an impressive undertaking that will contribute to public health for years to come. Initial PURE findings challenge conventional diet–disease tenets that are largely based on observational associations in European and North American populations, adding to the uncertainty about what constitutes a healthy diet. This uncertainty is likely to prevail until well designed randomised controlled trials are done. Until then, the best medicine for the nutrition field is a healthy dose of humility.

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